SYNOPSIS

SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY OF FUNCTIONALIZED PYRIDO[1,2- a]PYRIMIDINE-2-ONES

SUBMITTED BY

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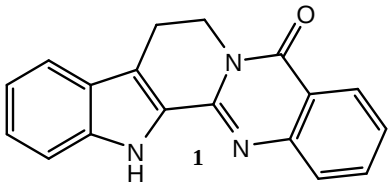
INTRODUCTION

The field of heterocyclic chemistry has long been presented as a special problem for chemists. The chemistry of heterocyclic compounds and methods for their synthesis form the back rock of modern medicinal, chemical and pharmaceutical research. The emergence of drug resistant bacteria has posed a growing challenge to the search for new chemical entities.

Nitrogen heterocycles of different ring sizes with different substitution patterns embedded in various molecular frame works constitute extremely important structural class in the search for bioactivity. The bridgehead nitrogen heterocycles are important class of hetrocyclic compounds because of their wide use in medicinal and agro chemistry as scaffolds for active agents such as antiviral, antiulcer, anti malarial, antibacterial, antifungal herbicidal, anti leprotic and immune suppressive agents. Saturated and partially saturated bicyclic 6-6 systems with one ring junction and one extra nitrogen atom viz pyrido[1,2-a] pyrimidines, pyrimido[1,2-a] pyrimidines and pyrazino[1,2-a] pyrimidines occur in many natural and biologically active compounds.

Over the last 84 years and from the time when Tschitschibabin prepared 2-hydroxy-4H –pyrido[1,2-a] pyrimidine-2,4-dione under the name of malonyl α amino pyridine, many synthetic and reaction studies have been carried out to deal with its derivatives. Pyrido[1,2-a] pyrimidine forms a key intermediate for the synthesis of the natural product rutecarpine(1) and some of their derivatives are neutral hydrogen chloride acceptors in organic synthesis.



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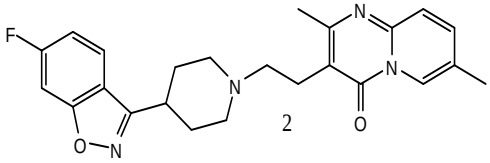
Pyrido[1,2-a] pyrimidine core has been a successful motif for the development of biologically interesting molecules including risperidone(2) & paliperidone(3) antipsychotic agent, metreperone(4) a selective $5HT_2$ receptor antagonist and lusaperidone(5) an antidepressant.



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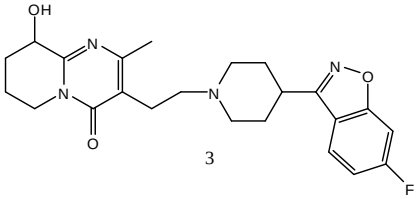

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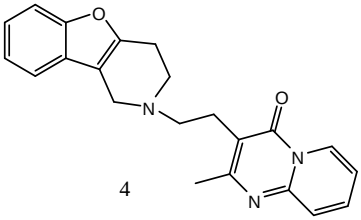

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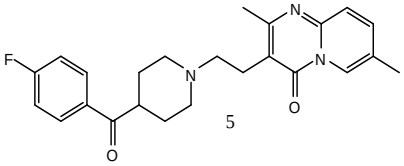

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Hence an attempt has been made to develop simple and high yielding synthetic routes for these biologically diverse compounds from readily available reagents.

A number of methods have been accomplished to synthesize pyrido[1,2-a] pyrimidines-4-one but only a few methods had been reported for the synthesis its regio isomer, pyrido[1,2-a] pyrimidines-2-one. The need to use high temperatures and pressure, lack of regio control in the reaction conditions, low yields and formation of significant amount of byproducts emphasizes the drawback of these methods.

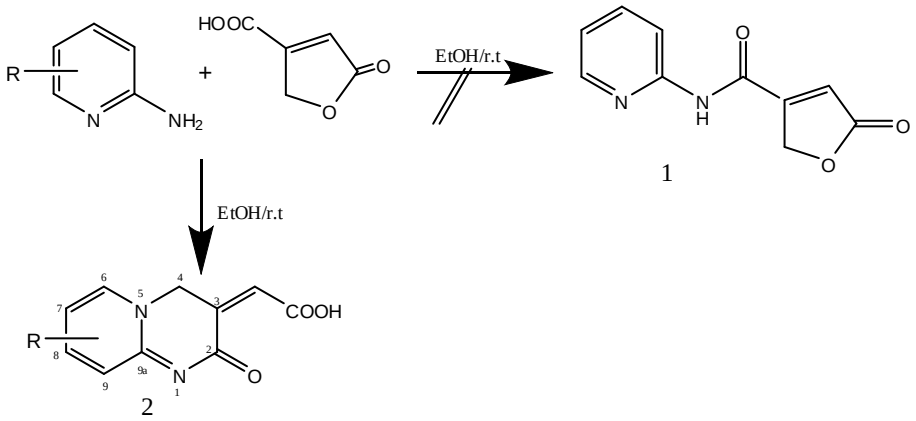
With the goal of devising a milder and more general method of synthesizing functionalized pyrido[1,2-a]pyrimidin-2-ones the following objectives were set forth.

- To develop a simple method for the synthesis of pyrido pyrimidine acetic acid derivatives using aconic acid and 2-amino pyridine as starting compounds.
- To characterize the compounds with IR, NMR and Mass Spectra.
- To further confirm the structure using COSY, HETCOR, & HMBC studies.
- To carry out some of the reactions and characterize them**.**
- To carry out anti-cancer and anti-bacterial studies for some of the synthesized compounds.
- To calculate clog P values and drug likeliness properties using Chemdraw ultra 10.0 , OSIRIS and Molinspiration software's.

SALIENT FEATURES OF THE RESEARCH WORK

The results pertaining to the present work entitled “Synthesis, Reactions & Biological Activity of Functionalized pyrido[1,2-a]pyrimidine-2-ones” are summarized below:

Scheme – I – Synthesis of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid.



R= H, 6Me, 7Me, 8Me, 9Me

The reaction was carried out by adding slowly the solution 2- amino pyridine in ethanol to aconic acid in ethanol. The reaction proceeded spontaneously in alcohol at room temperature and was complete with in few hours with excellent yields. ^{1}H spectrum displayed six signals and ^{13}C ten signals respectively. The mass spectrum of the compound (2) (R=H) showed M^{+} peak at m/z 204. All these data were in accordance with the proposed structure (1) and (2). Analysis of the IR spectrum revealed the absence of the N**H**-CO linkage as in the open chain amide (1). In the IR spectrum intense bands were observed at 3200cm^{-1}(broad), 1741cm^{-1}, 1670cm^{-1} and 1394cm^{-1}. N-**H** in plane bend at 1570-1515cm^{-1} and N-H out of plane bend at 750 - 680cm^{-1} were found to be absent. Hence cyclised product (2) itself had been obtained surprisingly. The bands at 3200cm^{-1}(broad), along with the band at 1670cm^{-1} and 1394cm^{-1} inferred the presence of the acid moiety in the compound. This was also confirmed by the presence of (M-44) peak at m/z 160 in the mass spectrum. Hence it was concluded that

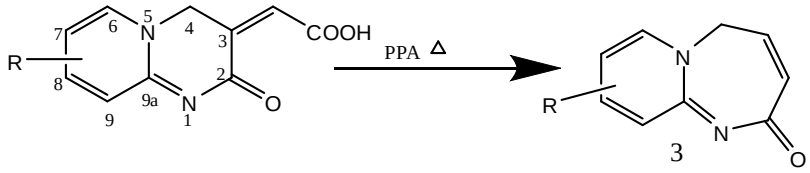
the cyclisation have occurred even in the first step itself and the compound obtained was (2) and not (1).

As expected a strongly deshielded aromatic proton at the 6th position due to the anisotropy of the carbonyl group at the 4th position was not observed in the ^{1}H NMR spectrum which indicated that the product formed was the 2-oxo isomer and not the 4-oxo isomer. A long range $^{3}J_{CH}$ correlation between the H_6 and C_4 carbon was also found to be absent in the HMBC spectrum which confirmed the formation of 2-oxo isomer. Hence the compound was identified as 2-oxo-2H-pyrido [1,2-a]pyrimidin-3(4H)-ylidene)acetic acid.

REACTIONS

1. WITH POLYPHOSPHORIC ACID

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid was treated with PPA for two hours. After the completion of the reaction as checked by TLC, the reaction mixture was poured into crushed ice, and neutralized with strong ammonia solution. A white precipitate settled down which was filtered and washed with ice cold water.



R= H, 6Me, 7Me, 8Me, 9Me

The FTIR spectrum of the compound (3) (R=H) showed bands at 3421, 1652, 1583cm^{-1}, which were attributed to the C-H aromatic and C=O moiety of the pyrimidine ring.

^{1}H NMR spectrum exhibited peaks at δ 4.5, 6.2, 6.9, 7.2, 7.6, 8.2 & 8.4. ^{13}C spectrum displayed nine signals at δ52,113,119,137,128,144,147,152 &170 respectively. Mass spectrum registered M^{+} peak at m/z 160. These facts clearly indicated that decarboxylation with ring expansion could have occurred during the reaction.

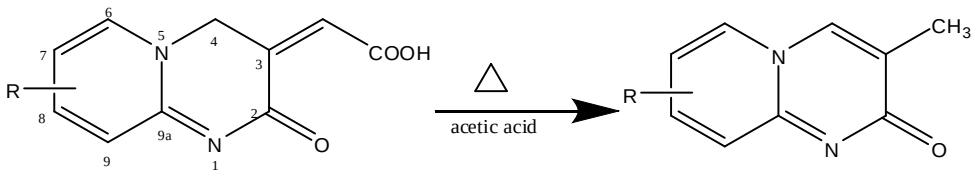
The following significant predictions were also made from the spectral analysis of the product,

- Dept – 135 spectrum indicated the presence of six methine carbons and one methylene carbon. Hence of the nine carbon atoms two carbons must be quaternary.
- The signal at δ167 disappeared which was originally assigned to the –COOH carbon in the compound(2)

  Comparison of the spectral data of the product showed the presence of only two quaternary carbon atoms instead of four as in (2). Also the number of methine carbon has increased from five to six. Hence, among the four quaternary carbons in the 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid one carbon could have left as CO_2 and the carbon at δ164 has been protonated. This has also been confirmed by the shift in the value of ^{13}C chemical shift of the sp^3 hybridized carbon atom from δ73 in the case of (2) to δ 52 in the product (3). Due to alpha effect, a shift of δ20 will be observed in sp3 hybridized carbon attached to =CH in α position. Therefore it was presumed that a methine group has been attached to the methylene carbon resonating at δ73. Furthermore, the ^1H NMR spectrum exhibited a very characteristic splitting pattern (i.e.) a doublet of triplet at δ6.2 & δ7.2 integrating for one proton each respectively. This fact confirmed that the compound possesses a (-CH_2-C**H**=C**H**-) moiety. This was also confirmed by HMBC spectrum. Hence the compound was found to be pyrido[1,2-a][1,3] diazepine-2(5H)-one. Mechanistic interpretation of the reaction was also attempted.

2. WITH ACETIC ACID

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid was treated with acetic acid in a steam bath. After the completion of the reaction, as noted by TLC the product was worked up and crystallised.



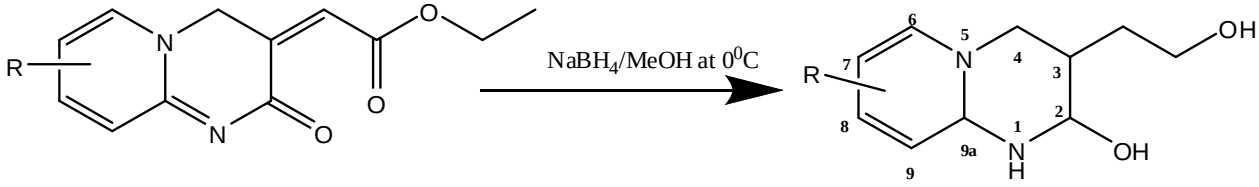
R= H, 6Me, 7Me, 8Me, 9Me

The structure of the compound was confirmed by ^{1}H and ^{13}C NMR analysis. $^{1}HNMR$ of the product (5) revealed a specific sharp singlet for three protons at $\delta 2.2$. This confirmed the presence of $-CH_3$ moiety in the product. For other products from methyl substituted pyridine rings an extra methyl signal appeared as singlet in the range of $\delta 2 - 2.3$. The other signals at $\delta 9.3$, 8.2, 7.7 and 7.6 were due to the aromatic region of the pyrimidine nucleus. Furthermore the ^{13}C spectrum accounted only for nine carbons instead of expected ten carbons indicating the occurrence of decarboxylation. Hence the compound was identified as 3-Me-pyrido-[1,2-a] pyrimidine 2-one. The reaction was rationalized mechanistically.

3. REDUCTION

3.A. REDUCTION WITH SODIUM BORO HYDRIDE

Reduction of Ethyl -2(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylideneacetate (R=H),with sodium borohydride in methanol at 0^0C afforded 3-(2-hydroxyethyl)-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol with lower melting points and with low yields(28-32%).



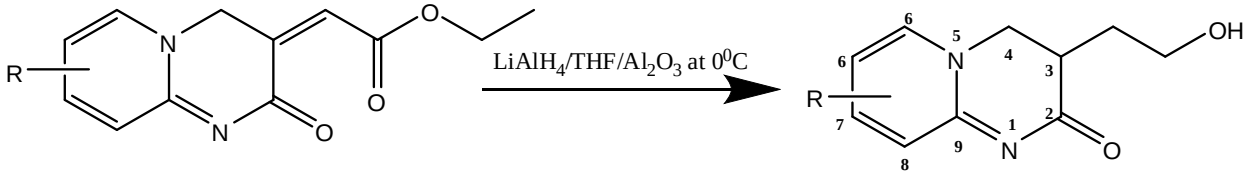
R= H, 6Me, 7Me, 8Me, 9Me

Since the yield of the reaction was low and formation of the byproducts was greater, the reaction was also carried out in presence of micellar media to improve the yields and selectivity of the reaction. As expected, the yield and selectivity of the reaction increased.

3.B. REDUCTION WITH LITHIUM ALUMINIUM HYDRIDE

The reduction of the Ethyl -2(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetate(R= H) was also carried out in the presence of $LiAlH_4$/THF at 0^0C which yielded

2-hydroxyethyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. The TLC showed too many spots. Even the major product could not be isolated. Hence the reaction was carried out in presence of activated alumina. This significantly reduced he formation of byproduct and the product was isolated with approximately 50-55% yield.



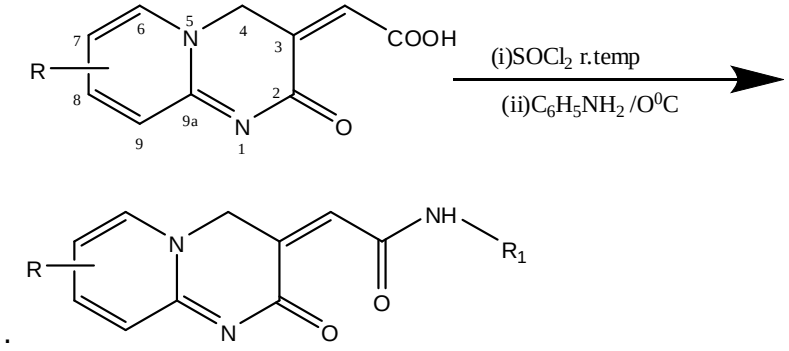
R= H, 6Me, 7Me, 8Me, 9Me

4. SYNTHESIS OF SERIES OF N-ARYL AMIDES

Synthesis of series of N-aryl amides of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid was carried out in two steps, viz

(i) Conversion of acid to acid chloride using thionyl chloride

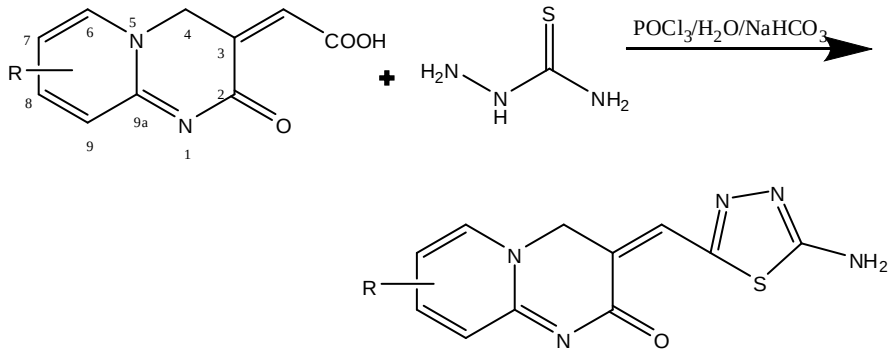
(ii) Treatment of acid chloride with various amines to afford N-arylamides with moderate yields.



R= H, 7Me, ;R_1= aniline, p-anisidine, p-toluidine, o,p-dimethoxy aniline, p-chloro aniline, benzyl amine, adenine, benzimidazole

5. WITH THIO SEMICARBAZIDE

The thiadiazole derivatives of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acids were prepared by the reaction of the acid with thiosemicarbazide in $POCl_3$, followed by the neutralization with sodium bicarbonate in good yields.



R= H, 6Me, 7Me, 8Me, 9Me

BIOLOGICAL STUDIES OF THE SYNTHESISED COMPOUNDS

In vitro anticancer studies on human cervical cancer cell lines were carried for two of the synthesized amides. The two compounds were found to inhibit the cell growth with 80mM concentration

Anti bacterial activities (gram positive and gram negative) were studied for the synthesized acids and thiadiazole derivatives.

The logP values were calculated using Chemdraw ultra10.0, Osiris and molinspiration softwares for the following compounds

- 2- oxo Pyrido[1,2-a] pyrimidin-3(4H)-Ylidene acetic acid
- N-aryl amides of pyrimidine acetic acid
- Thiazoles of pyrimidine acetic acid

The logP values for the above compounds lie between 0.5 -2.

Thus a simple method have been evolved for the synthesis of various functionalized pyrido[1,2-a] pyrimidine-2-ones which would perhaps prove to be potential drugs.

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